


Posebnosti arterijske hipertenzije u žena i povezanost s oštećenjem ciljnih organa

Unique Characteristics of Hypertension in Women and Association with to Target Organ Damage

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SAŽETAK: Tradicionalni čimbenici rizika za oštećenje ciljnih organa jednaki su za muškarce i žene i uključuju arterijsku hipertenziju, hiperlipidemiju, šećernu bolest, nikotinizam i fibrilaciju atrijske. No postoje i specifični rizični čimbenici prisutni samo u žena koji uključuju razlike u spolnim hormonima, estrogenskoj dodatnoj terapiji i doba trudnoće. Potrebna su daljnja istraživanja koja će pridonijeti boljem razumijevanju specifičnosti vezanih za zdravlje žena, što će dodatno utjecati na sigurnosti i učinkovitosti primijenjenih terapijskih mogućnosti.

SUMMARY: Traditional cardiovascular risk factors for target organ damage are the same in both women and men and include hypertension, hyperlipidemia, diabetes mellitus, smoking, and atrial fibrillation. There are several risk factors that are specific to women, such as differences in sex hormones, exogenous estrogens, and pregnancy. Further investigation into the sex-specific differences in therapeutic utilization and the sex-specific differences in the safety and efficacy of the therapeutic options is required.

KLJUČNE RIJEČI: žene, čimbenici rizika, arterijska hipertenzija.

KEYWORDS: women, risk factors, hypertension.

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Razlike između muškarca i žena u području hipertenzije nisu novost. Postoje poznate razlike u prevalenciji koja se očituje dobom razlikom (višom prevalencijom u muškaraca do petog desetljeća života, a u kasnijoj dobi višom prevalencijom u žena) i višom učestalosti sindroma „bijeke kute“ u žena, no manje je poznat učinak hipertenzije na oštećenje ciljnih organa, posebice moždanog udara koji je češći u žena nego u muškaraca¹.

Unatoč jasnoj biološkoj različitosti žena i muškaraca, ne postoje smjernice vezane za spolne razlike, osim za liječenje hipertenzije u trudnoći¹. Hipertenzija je stanje endotelne disfunkcije svih žila, a uz pretilost je najvažniji čimbenik rizika za razvoj bolesti srca i bubrega^{2,3}. Cjelovita problematika žene kao bolesnice ističe se posebice u razdoblju trudnoće s potrebnosti multidisciplinarnoga pristupa.

Autoimunosne bolesti u žena, posebice tipa sustavnog lupusa, često su povezane s bubrežnim oštećenjem. Bolesnice s autoimunskim

Differences between men and women in hypertension are not recent news. There are well-established differences in prevalence which manifests in age difference (higher prevalence in men up to the fifth decade of life and higher prevalence in women in later ages) as well as higher incidence of white coat hypertension in women; however, the effect of hypertension on target organ damage is less well known, particularly for stroke, which is more common in women than in men¹.

Despite a clear biological difference between women and men, there are no guidelines related to the sex differences except for the treatment of hypertension in pregnancy¹. Hypertension in a state of endothelial dysfunction of all blood vessels, and obesity represents the most important factor for the development of heart and kidney disease^{2,3}. The overall challenges with female patients are especially emphasized in pregnancy, requiring a multidisciplinary approach.

Autoimmune diseases in women, especially systemic lupus types, are often associated with

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bolestima imaju povišen rizik od kardiovaskularnih bolesti, pa je stoga suradnja različitih struka u liječenju žena s ovim bolestima osobito važna⁴. Zatajivanje srca s očuvanom sistoličkom funkcijom češće je u žena, a znamo koliko je važna poveznica srca i mozga⁵.

Bubrežno-srčano-moždana poveznica u žena

Određnica moderne terapije arterijske hipertenzije koja je sveprisutan i aktualan preventabilni uzrok jest smanjenje ukupne smrtnosti. Često zaboravljamo da je moždani udar treći vodeći uzrok smrti u žena u Sjedinjenim Američkim Državama i vodeći uzrok nesposobnosti⁵. Uz tradicionalne čimbenike rizika za oštećenje ciljnih organa koji su jednaki za muškarce i žene (arterijska hipertenzija, hiperlipidemija, šećerna bolest, nikotinizam, fibrilacija atrijsa) postoje i specifični čimbenici rizika prisutni samo u žena (razlike u spolnim hormonima, estrogenskoj dodatnoj terapiji i doba trudnoće)⁵.

Kardiovaskularne bolesti (KVB) odgovorne su za više od 17 milijuna smrtnih slučajeva godišnje⁶. Ukupni podatci pokazuju da od KVB-a umire više žena nego muškaraca. Ova skupina bolesti odgovorna je za 45 % svih smrti žena te 38 % svih smrti muškaraca. Svjetska zdravstvena organizacija objavila je 2013. godine da je arterijska hipertenzija odgovorna za najmanje 45 % smrtnih slučajeva zbog bolesti srca i 51 % smrtnih slučajeva zbog moždanog udara, a svaka deseta osoba ima i kroničnu bubrežnu bolest (KBB)⁶. Rizik od razvoja KBB-a u žena je viši nego u muškaraca (14 % prema 12 %)⁷. Kronična bubrežna bolest pogađa oko 195 milijuna žena u svijetu i osmi je vodeći uzrok smrti žena s godišnje 600 000 smrtnih slučajeva⁸. Ženski spol, arterijska hipertenzija, starija dob i pretilost obilježja su srčane slabosti uz očuvanu sistoličku funkciju (HFpEF)^{9,10}. Svakodnevno se susrećemo s bolesnicima koji imaju hipertenzijom remodelirano srce s fibrilacijom atrijsa i potrebnosti usklađivanja doza oralnih antikoagulanata s obzirom na stupanj KBB-a među kojima je sve veća učestalost žena starije životne dobi¹⁰. Osim toga, HFpEF se većinom neadekvatno prepoznaje i zbrinjava, a udružena je s brojnim pridruženim stanjima poput hipertenzije (60 - 80 %), ishemijske bolesti srca (35 - 70 %), šećerne bolesti (20 - 45 %) i fibrilacije atrijsa (15 - 40 %)¹¹.

Stoga se zadnjih desetak godina ističe povezanost KBB-a, kardiovaskularnog pobola i smrtnosti te mogućnosti preventabilnih mjera koja preporučuju različita društva, poput osnivanja *The Council on Kidney in Cardiovascular Disease*, u sklopu *American Heart Association* koji pristupa problemu bubrežne bolesti kao dijelu translacijske medicine sa svrhom smanjenja kardiovaskularnog rizika.

Pretilost, bubrežno oštećenje i hipertenzivni poremećaji u žena

Prevalencija pretilosti u Europi je između 4 i 28 % u muškaraca i 6,2 i 36,5 % u žena. Nevjerojatno je da je debljina češća u žena nego u muškaraca. Učestalost debljine raste s dobi (25 % osoba između 45. i 72. godine je pretilo). Ono što zabrinjava jest visoka učestalost debljine u mlađim dobnim skupinama, posebice u dječjoj dobi (8,8 %). Dobro je poznata činjenica da su u pretilih bolesnika povišeni kardiovaskularna smrtnost i pobol, kao i povezanost s nekontroliranom hipertenzijom².

kidney damage, and patients with autoimmune diseases have increased risk of cardiovascular diseases; consequently, the cooperation between different fields of expertise in the treatment of women with autoimmune diseases is especially important⁴. Heart failure with preserved ejection fraction is more common in women, and the importance of the link between the heart and the brain is well-known⁵.

The kidney-heart-brain link in women

The guiding principle of arterial hypertension treatment, an omnipresent and current preventable causal factor, is the reduction of total mortality. We often forget that stroke is the third leading cause of death for women in the United States of America and the leading cause of incapacitation⁵. Beside traditional risk factors for target organ damage that are the same for men and women (arterial hypertension, hyperlipidemia, diabetes, cigarette smoking, atrial fibrillation), there are also specific risk factors present only in women (differences in sex hormones, estrogen supplementation therapy, and pregnancy)⁵.

Cardiovascular diseases (CVD) are responsible for more than 17 million cases of death per year⁶. The overall data show that more women than men die of CVD. This group of diseases is responsible for 45% of all deaths in women and 38% of all deaths in men. In 2013, the World Health Organization published findings showing that arterial hypertension is responsible for at least 45% of cases of death due to heart disease and 51% cases of death due to stroke, and that every tenth person also has chronic kidney disease (CKD)⁶. The risk of development of CKD in women is higher than in men (14% vs. 12%)⁷. Chronic kidney disease affects approximately 195 million women worldwide and is the 8th leading cause of death in women annually, with 600 000 cases of death⁸. Female sex, arterial hypertension, advanced age, and obesity are characteristic for heart failure with preserved ejection fraction (HFpEF)^{9,10}. In everyday practice, patients with heart remodeling due to hypertension with atrial fibrillation are common and require adjustment of oral doses of anticoagulation medication depending on the level of CKD, with an increasing prevalence of women of advanced age among them¹⁰. Additionally, HFpEF is often inadequately recognized and managed, and it is associated with numerous comorbid states such as hypertension (60%-80%), ischemic heart disease (35%-70%), diabetes (20%-45%), and atrial fibrillation (15%-40%)¹¹.

Consequently, there have been efforts to raise awareness of the association between CKD, cardiovascular morbidity and mortality, and the possibility of preventive measures recommended by various societies, such as the formation of the *Council on Kidney in Cardiovascular Disease* as part of the *American Heart Association*, which approaches the issues of kidney disease as a part of translational medicine with the goal of reducing cardiovascular risk.

Obesity, kidney damage, and hypertensive disorders in women

The prevalence of obesity in Europe is between 4-28% in men and 6.2%-36.5% in women. It is incredible that obesity is more common in women than in men. The prevalence of obesity increased with age (25% of persons between 45 and 72 years of age are overweight). What is worrying is the high prevalence of obesity in younger age groups, especially in childhood (8.8%). It is a well-known fact that cardiovascular mor-

Osobitost poremećaja vezanih za debljinu jest mehanizam inzulinске rezistencije kao i ekotopična akumulacija masnoća koja pridonosi oštećenju organa u kontekstu metaboličkih bolesti, pokazujući da bi bubrežna bolest vezana za debljinu zapravo stanje lipodistrofije i ubrzanog procesa starenja. Povezanost poremećenog lipidnog metabolizma, inzulinске rezistencije i aktivacija upalnoga procesa uzrokuje razvoja glomerulopatije povezane s debljinom i srčanog te vaskularnog remodeliranja². Hipertenzivni su poremećaji prepoznati kao važan čimbenik rizika od KVB-a u žena¹².

Potrebno je razlikovati nekoliko specifičnih stanja.

1. Žene na oralnoj kontraceptivnoj terapiji

Uzimanje oralnih kontraceptiva povezano je s malim, ali znatnim porastom arterijskoga tlaka (AT) i hipertenzijom u 5 % korisnica oralne kontraceptivne terapije (posebno starije generacije)¹³. Incidencija infarkta miokarda i ishemijskog moždanog udara niska je u dobnoj skupini žena koje se koriste oralnom kontracepcijom. Smjernice ne preporučuju primjenu oralne kontraceptivne terapije u žena koje imaju nekontroliranu hipertenziju, a rizik za razvoj hipertenzije smanjuje se prestankom uzimanja takve terapije¹⁴.

2. Žene na hormonskom nadomjesnom liječenju

Niska je vjerojatnost da će AT porasti u menopauzalnih hipertenzivnih žena koje su na hormonskoj nadomjesnoj terapiji¹⁵. Hormonska nadomjesna terapija i selektivni modulatori estrogenskih receptora ne preporučuju se za primarnu i sekundarnu prevenciju KVB-a.

3. Specifičnost žena i smjernice za hipertenziju u trudnoći

Nema specifičnih smjernica za liječenje arterijske hipertenzije u žena, osim u trudnoći. Smjernice ESH/ESC-a za liječenje hipertenzije iz 2013. godine preporučuju početak antihipertenzivne terapije pri vrijednosti AT-a >140/90 mmHg u žena s gestacijskom šećernom bolesti, preegzistirajućom hipertenzijom uz pojavu gestacijske hipertenzije i u onih s hipertenzijom s asimptomatskim organskim oštećenjima ili simptomima kroz bilo koje razdoblje trudnoće¹⁴. Izbor lijekova za liječenje hipertenzije u trudnoći jesu metildopa, labetalol i nifedipin (dugodjelujući). U emergenciji kao što je teška preeklampsija lijek izbora jest intravenska primjena labetalola¹⁴. U žena s preeklampsijom rizik od razvoja hipertenzije u kasnijoj je dobi četiri puta veći nego u žena koje nisu imale preeklampsiju¹⁶. Najnovija literatura navodi preeklampsiju kao rani biljeg rizika od KVB-a. Žene koje su imale preeklampsiju imaju dvostruko veći rizik za razvoj ishemijske bolesti srca, moždanog udara i tromboembolijskih bolesti u razdoblju od 5 do 15 godina nakon trudnoće¹⁷. Komplikacije povezane s trudnoćom povisuju i rizik od bubrežne bolesti. Preeklampsija, septični pobačaj i stanja upala poput akutnog ili kroničnog pijelonefritisa te autoimunskih bolesti kao što je lupusni nefritis tipično se pojavljuju u žena i vodeći su uzroci akutnoga bubrežnog oštećenja bubrega u žena⁴.

4. Kronična bubrežna bolest u žena

Kronična bubrežna bolest koja danas ima sve više pandemijske razmjere jest dodatni čimbenik rizika smanjene plodnosti i nepovoljnog ishoda trudnoće, a žene s KBB-om u povišenom su riziku za loš ishod zbog mnogo češće pojavnosti hipertenzije i prijevremenog porođaja¹⁸. Napredovanjem KBB-a, uz brojne poremećaje drugih tjelesnih sustava, u žena se pojavljuju i poremećaji menstruacije, neplodnost i rana menopauza. Žene s preuranjenom menopauzom u povišenom su riziku od razvoja KVB-a¹⁹.

tality and morbidity as well as association with uncontrolled hypertension is higher in obese patients².

The specific characteristic of disorders related to obesity is the mechanism of insulin resistance and ectopic lipid accumulation, which contributes to organ damage in the context of metabolic diseases, indicating that kidney disease associated with obesity is really a state of lipodystrophy and aging process acceleration. The association between lipid-disordered metabolism, insulin resistance, and the activation of inflammatory processes leads to the development of glomerulopathy associated with obesity and heart and vascular remodeling². Hypertensive disorders have been recognized as an important risk factor for CVD in women¹².

It is important to differentiate between several specific states:

1. Women receiving oral contraceptive therapy

Taking oral contraceptives is associated with a small but significant increase in blood pressure (BP) and hypertension in 5% of women receiving oral contraceptive therapy (especially at older ages)¹³. The incidence of myocardial infarction and ischemic stroke is low in the age group of women using oral contraceptives. Guidelines do not recommend the use of oral contraceptives in women who have uncontrolled hypertension, and the risk of developing hypertension is reduced with the cessation of oral contraceptives¹⁴.

2. Women on hormone replacement therapy

There is a low probability of BP rise in menopausal hypertensive women receiving hormone replacement therapy¹⁵. Hormone replacement therapy and selective estrogen receptor modulators are not recommended for primary and secondary prevention of CVD.

3. Specific characteristics in women and guidelines for hypertension in pregnancy

There are no specific guidelines for the treatment of arterial hypertension in women except in pregnancy. The ESH/ESC guidelines for the treatment of hypertension from 2013 recommend commencing antihypertensive treatment at BP values >140/90 mmHg in women with gestational diabetes, preexisting hypertension with the manifestation of gestational diabetes, and in those with hypertension with asymptomatic organ damage or symptoms in any period of the pregnancy¹⁴. The choice of medication for the treatment of hypertension in pregnancy are methyldopa, labetalol, and nifedipine (long-acting). In emergencies such as severe preeclampsia, the medication of choice is the intravenous application of labetalol¹⁴. In women with preeclampsia, the risk of developing hypertension in older age is four times higher in comparison with women who did not have preeclampsia¹⁶. The newest literature lists preeclampsia as an early marker of CVD risk. Women who had preeclampsia have double the risk of developing ischemic heart disease, stroke, and thromboembolic diseases in a period of 5-15 years after pregnancy¹⁷. Complication associated with pregnancy also increase the risk of kidney disease. Preeclampsia, septic abortion, and inflammatory conditions such as acute or chronic pyelonephritis and autoimmune diseases such as lupus nephritis typically manifest in women and are the leading cause of acute kidney damage in women⁴.

4. Chronic kidney disease in women

Chronic kidney disease, which is currently reaching increasingly pandemic proportions, is an additional risk factor for reduced fertility and unwanted outcomes in pregnancy,

Zaključak

Važno je navesti da su žene mnogo manje zastupljene u nizu kardiovaskularnih istraživanja, posebice onih vezanih za smjernice²⁰, pa se stoga postavlja pitanje jesu li postojeće smjernice prikladne za liječenje žena ili su dostatne samo za muškarce. Žene češće nego muškarci umiru od KVB-a, a rizik je od razvoja KBB-a u žena viši nego u muškaraca. Već u početnim stadijima KBB nosi povećan kardiovaskularni rizik, a u osnovi KVB-a jest disfunkcija endotela s istodobnim promjenama u bubrežnoj i koronarnoj mikrocirkulaciji. Potrebna su daljnja istraživanja koja će pridonijeti boljem razumijevanju specifičnosti vezanih za zdravlje žena, što će dodatno utjecati na sigurnosti i učinkovitosti primijenjenih terapijskih mogućnosti.

and women with CKD are at increased risk of poor outcomes due to greatly increased incidence of hypertension and pre-term births¹⁸. The progression of CKD in women, in addition to numerous disorders of other bodily systems, also leads to menstruation disorders, infertility, and early menopause. Women with premature menopause are at higher risk of developing CKD¹⁹.

Conclusion

It is important to note that women are far less represented in a number of cardiovascular studies, especially those related to guidelines²⁰, which begs the question whether the existing guidelines are adequate for the treatment of women, or only for the treatment of men. Women die more often from CVD than men, and the risk of CKD in women is higher than in men. Even in the early stages, CKD has increased cardiovascular risk, and CVD is basically endothelial dysfunction with simultaneous changes in renal and coronary microcirculation. Further studies are needed to contribute to a better understanding of the unique characteristics related to female health, which have an additional influence on the safety and effectiveness of the treatment options being applied.

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